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Use of Acid-Suppressive Drugs in Pregnancy and the Risk of Childhood Asthma: Bidirectional Crossover Study using the General Practice Research Database

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Abstract

Background Recent studies have reported an association between maternal use of gastric acid-suppressive drugs during pregnancy and asthma in the offspring, but the association could have been confounded by unmeasured risk factors.

Objective We assessed the association between the use of acid-suppressive drugs during pregnancy and the risk of developing childhood asthma using a bidirectional crossover design.

Methods Mother–infant matched sets in the UK General Practitioners Research Database were used to identify children with a drug-treated asthma diagnosis during the years 2006–2010 who were matched to a sibling without asthma as controls. Primary exposure was use of any anti-suppressive drug during pregnancy, and subgroup analyses

were conducted according to drug class (e.g. proton pump inhibitors or histamine 2 receptor antagonists) and trimester. Conditional logistic regression was used to estimate odds ratios (OR) with their corresponding 95 % confidence intervals (CIs).

Results A total of 1,874 children with asthma and 1,874 control siblings were included in the analysis. The exposure rate among case and control pregnancies was 22 and 20 %, respectively. After adjustments for gender, birth order, mother's age and general practice visits, the exposure to any gastric-acid suppressive drug during pregnancy slightly increased the risk for developing asthma (OR 1.23, 95 % CI 1.01–1.51; $p = 0.042$). A trend towards increased risks was observed for those who used proton pump inhibitors and/or histamine 2 receptor antagonists (adjusted OR 1.72, 95 % CI 1.00–2.98; $p = 0.048$).

Conclusions These findings lend support to the emerging evidence that exposure to acid-suppressive drugs during pregnancy is associated with childhood asthma. More basic research is now warranted to investigate the mechanisms.

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1 Introduction

Asthma is a prevalent disease in childhood and a significant cause of morbidity [1]. In the UK, it has been estimated that up to 11 % of all children have one or more allergic diseases, asthma being a common disease entity [2]. Importantly, asthma incidence has increased over decades, with large variations between countries, suggesting that increased exposure to environmental factors may play a role [3, 4]. Lately, there has been an interest in the role of the prenatal environment in the aetiology of asthma [5]. Epidemiological studies have suggested that the key time period for childhood allergies and asthma development

occurs between conception and early childhood, and prenatal drug use has also been implicated [6, 7].

During pregnancy gastrointestinal symptoms are common, and proton pump inhibitors (PPIs) and histamine 2 receptor antagonists (H2ra) and, to a lesser extent, other antacids are effective against such symptoms [8]. Dehlink and colleagues [9] were the first to hypothesize that the use of acid-suppressive therapy during pregnancy may cause the development of asthma in offspring. The investigators found that exposure to acid-suppressive drug therapy was associated with development of childhood asthma, with a statistically significant odds ratio (OR) of 1.51, but residual confounding by unmeasured risk factors could not be ruled out. Andersen and colleagues [10] followed up on this study and reported an increased risk of childhood asthma after in-utero exposure to PPIs in a cohort of Danish women, with an estimated OR of 1.41. Because the observed association was not drug specific and was also observed for maternal postnatal use, the authors stated that the association could be explained by a 'class effect' or underlying maternal condition. Recently, Källén and colleagues [11] also observed an increased risk between drugs for gastroesophageal reflux in pregnancy and childhood asthma (adjusted OR 1.32), but asthma in the mother could have confounded the association. Prior to the current study, we conducted a crossover and case-control study in The Netherlands using the University of Groningen mother–infant drug prescription database, which yielded results for use of either PPIs or H2ra similar to those in the earlier studies, but asthma could only be defined by the presence of respiratory prescriptions [12].

The study of drug therapy in pregnancy and subsequent risks of asthma in the offspring is complicated. The development of asthma depends on a complex interaction between genetic and various environmental risk factors. For example, the presence of asthma in the mother, life-style factors such as smoking during pregnancy, or pre-term delivery all have been found to increase the risk of asthma [13]. The distribution of these potential risk factors may well be different between pregnant women who use acid-suppressive drug therapy and those who do not, and this may lead to confounding bias [14]. We designed a study to further evaluate acid-suppressive drug use during pregnancy and development of childhood asthma in the offspring where the potential for confounding bias was limited through the use of a bidirectional crossover design.

2 Methods

2.1 Setting and Study Design

This crossover study was conducted using data from the UK General Practice Research Database (GPRD), which is

administered by the Medicines and Healthcare Products Regulatory Agency and has been previously described in detail [15–17]. In brief, the GPRD contains electronic medical records for a nationally representative group of British residents currently enrolled in more than 450 general practice offices in the UK. General practitioners (GPs) who participate in the GPRD have agreed to provide patient data for research purposes and are trained to accurately record information about patient demographics, medical diagnoses and procedures that are part of routine care or resulting from hospitalizations, results of laboratory and pathology testing, and referrals to hospitals and specialists. In the UK, 'Read' codes, which are more extensive than the ICPC (International Classification of Primary Care) coding system and agree with the International Classification of Diseases, tenth revision (ICD-10) classification system, are used by GPs to classify medical diagnoses. The quality and completeness of the information recorded in the GPRD has been widely validated [15–17]. We linked mothers within the GPRD to their children using a unique family identification number and the dates of delivery in the mother's record in combination with the dates of birth in her children's records. This mother–baby linkage was used in a previous study on maternal drug exposures and asthma in the child [18].

We designed a non-traditional nested crossover study, which is a modification of the case-crossover design first introduced by Maclure in 1991 [19]. The conventional approach is to compare the exposure prior to the case-defining event with the same individual's exposure at referent time points when he or she did not experience the event. By making within-person comparisons, all measured and unmeasured time-invariant confounders are controlled for in the design. We adopted a 'bi-directional cross-over' design or 'within-mother-between-pregnancy' design [20–22] using sibling cases and controls born in different order from the same mothers to control for any bias by exposure trends within the traditional studies [22].

2.2 Source Population

The source population for the study comprised all mothers and their infants who were linked in the mother–infant subset of the GPRD. The study period for case detection covered the years 1996 through 2010. Mothers with multiple singleton births, who were aged between 15 and 40 years in the year of delivery of their first infant, were included. Mothers were required to have a recorded history of 12 months or more prior to the birth of their first child and to have at least two children. Each child was required to have at least 3 years of follow-up in the data after birth. Mothers who conceived a baby with a congenital birth defect or chromosomal anomaly or who had a history of

use of known teratogens, including antineoplastics, anti-convulsants, retinoids, angiotensin-converting enzyme inhibitors, anticoagulants, tetracyclines, antithyroid drugs and lithium, were excluded. Since teratogen use could seriously confound or modify our findings, we decided a priori not to include this relatively small group of women. All codes and relevant prescriptions are provided in the Appendix (see the Electronic Supplementary Material).

2.3 Case and Control Definition

Asthma cases were defined as children who received a first diagnosis of asthma any time between birth and 14 years of age (see the Electronic Supplementary Material for Read codes) and who were prescribed any asthma drug at least three times (see the Electronic Supplementary Material for prescription drugs) within 12 months after first asthma diagnosis date, which defined the index date. The minimum number of three prescriptions was included to reduce the chance of false-positive case selection. Pont et al. [23], for example, studied sensitivity, specificity and predictive values of drug medications for identifying patients with asthma. A prescription for one or more anti-asthma medications identified 95 % of patients with an asthma diagnosis (positive predictive value 0.70), while two or more anti-asthma medications identified 71 % (positive predictive value 0.79). Since asthma patients can be reliably identified from prescribing data, we decided to use a definition that was even more specific (three prescriptions instead of two prescriptions) to avoid including cases without asthma and to provide a clear comparison with controls with no asthma drugs or diagnosis codes. Children from the mother–infant subset who were born to the same mother as a case child (before or after) were used as controls if they had neither a history of childhood asthma nor any prescription for asthma in their medical history. The control siblings were required to be present in the database at an age similar to that of the case (± 1 year) at first diagnosis of asthma (index date). We included only mothers who had a pair of one eligible case and one eligible control. We excluded a few mothers ($N = 47$) who had more than one eligible control, e.g. twins, from further data analysis.

2.4 Exposure Status and Covariates

The exposure of interest was the prescription of any acid-suppressive drug therapy during pregnancy (see the Electronic Supplementary Material for specific drugs) defined as receipt of one or more prescriptions for any gastric acid-suppressive drug just prior to or during any trimester of pregnancy. We estimated the date of conception by subtracting 270 days from the delivery date because the date

of conception was unavailable. Exposure at any time during pregnancy was defined as 0–335 days prior to the delivery date to include drugs prescribed prior to conception that could have been taken during early pregnancy. Exposure during the first trimester was further classified as a prescription between 180 and 335 days prior to the delivery date, for the second trimester between 90 and 179 days, and for the third trimester between 0 and 89 days. Non-exposure was defined as absence of any prescription for an acid-suppressive drug during pregnancy (between 0 and 335 days prior to the delivery date). Exposure was further grouped into PPIs, H2ra, and other antacids; categories were not mutually exclusive. Women could have used more than one drug at the same time and/or during different trimesters. We also evaluated exposure according to trimester (first and second vs. third), since, patho-physiologically, lungs are being developed during the first and second trimester, whereas immune response matures toward the end of pregnancy.

Covariates in the study were selected on the basis of subject matter knowledge and previous studies on this topic [9–13]. We collected information on the child's gender and potential confounders such as age of the mother at delivery, birth order, body mass index (BMI), smoking status, presence of migraine, pre-eclampsia or the prescription of paracetamol or non-steroidal anti-inflammatory drugs (NSAIDs) during pregnancy, or any prescription for any acid-suppressive medication in the child prior to the index date. The number of practice visits prior to delivery was also recorded as a proxy for healthcare use. A diagnosis of preterm delivery or low birth weight was also recorded as an indicator of risks for asthma development.

2.5 Data Analysis

We conducted conditional logistic regression analyses to obtain ORs and their corresponding 95 % confidence intervals (CIs) of the association between PPI exposure in the mother and the diagnosis of childhood asthma. In the primary analysis, we first modeled the primary exposure-outcome association adjusted for confounders. Then, separate causal models were made for the explorative exposure-outcome associations. Confounders were selected if they were *both* associated with the outcome and the exposure on the basis of the p -value (< 0.05) or based on knowledge of the subject matter. To further address the potential for residual bias and effect modification, relevant explorative subgroup analyses without formal tests for interaction were conducted according to acid-suppressive drug type (PPI, H2ra and other) and trimester (first and second vs. third). We conducted the statistical analyses using the software program SAS, Version 9.1 (SAS Institute, Inc., Cary, NC, USA).

3 Results

We identified 1,874 mothers who had 1,874 children with asthma and one qualifying control sibling without asthma. The mean age of the mothers was 28.2 years and the mean age at first diagnosis of asthma in the offspring was 3.6 years. Cases were more often male and first born, and their mothers were statistically significantly younger during the case's pregnancy than during the control pregnancy and had fewer GP visits during the case pregnancy than during the control pregnancy (see Table 1). All other covariates were similarly distributed.

The distribution of covariates was similar in control children exposed to acid-suppressing drugs and those not exposed except for BMI, mother's age and paracetamol use. There was a significantly higher prevalence of high BMI and higher use of paracetamol and a near significant younger age of the mother in the exposed than in the unexposed pregnancies (see Table 2).

Twenty-two percent of children with asthma had mothers who were exposed to any acid-suppressive drug during pregnancy (see Table 3). The corresponding figure for the control group was 20 %. After adjustment for gender of the child, birth order, age of the mother and number of GP visits, the exposure to any acid-suppressive drug during pregnancy was associated with a small but statistically significant increased odds for developing childhood asthma (adjusted OR 1.23, 95 % CI 1.01–1.51; $p = 0.042$). Stratified analysis indicates that this effect was restricted to exposure in the third trimester (adjusted OR

1.29, 95 % CI 1.03–1.62; $p = 0.029$). Analyses according to subgroups of acid-suppressive drugs indicated that those who used PPIs and/or H2ra during pregnancy had higher risks of a child who developed asthma (adjusted OR 1.72, 95 % CI 1.00–2.98; $p = 0.048$). Though not statistically significant, the analysis of PPI use alone yielded the highest risk for asthma (OR 2.76, 95 % CI 0.98–8.17).

4 Discussion

4.1 Main Findings

These results suggest that the use of gastric acid-suppressive medications during pregnancy is associated with an increase in the risk for development of asthma in the child. The trend towards increased risk was present in children of women exposed to PPIs and/or H2ra and when the exposure occurred during the third trimester of pregnancy.

4.2 Strengths and Limitations

Major strengths of the study include the use of the widely researched GPRD, which contains accurate information on diagnoses and prescriptions and large numbers of patients. The GPRD also contains a family identification number, making it possible to link mothers and their infants. Further, using the cross-over design, we were able to control for many potential confounders inherent in observational studies of this topic. While mothers taking acid-suppressive

Table 1 Distribution of covariates in children with asthma (cases) and control siblings

	Cases (<i>N</i> = 1,874) <i>N</i> (%)	Controls (<i>N</i> = 1,847) <i>N</i> (%)	<i>P</i> -value
Child characteristics			
Male gender	1,110 (59)	843 (45)	<0.001
Mean age at first asthma diagnosis	3.6 years	NA	NA
Mean number of asthma drugs in 12 months	15	0	NA
First-born	991 (53)	728 (39)	<0.001
Use of antacids prior to index date	22 (1.2)	29 (1.7)	0.32
Low birth weight/prematurity	28 (1.5)	18 (1.0)	0.14
Pregnancy characteristics			
Mean age (SD) in years	27.9 (5.2)	28.6 (5.2)	<0.001
Presence of asthma	89 (5)	90 (5)	0.94
Presence of migraine	33 (2)	32 (2)	0.90
Presence of (pre-)eclampsia	1 (0.05)	0 (0)	0.32
High BMI (>35) ^a	148 (10)	165 (11)	0.39
Current smoker ^b	470 (29)	459 (28)	0.51
Mean number of GP visits during pregnancy	11.4 (7.4)	11.9 (7.6)	0.03
Use of paracetamol	256 (14)	259 (14)	0.89
Use of NSAIDs	49 (3)	50 (3)	0.91

BMI body mass index, GP general practitioner, NA not applicable, NSAIDs non-steroidal anti-inflammatory drugs, SD standard deviation

^a Data on BMI were missing for 877 patients

^b Data on smoking were missing for 528 patients

Table 2 Distribution of covariates in unexposed and exposed pregnancies estimated from control pregnancies in the crossover analysis ($N = 1,874$). Number (percentages) are given unless stated otherwise

	Unexposed pregnancies ($N = 1,507$) N (%)	Exposed pregnancies ($N = 367$) N (%)	P -value
Child characteristics			
Male gender	676 (45)	167 (46)	0.82
First-born	584 (39)	144 (39)	0.86
Use of antacids prior to index date	18 (1)	4 (1)	0.87
Low birth weight/prematurity	16 (1)	2 (0.5)	0.36
Pregnancy characteristics			
Mean age (SD) in years	28.5 (5.3)	29.0 (4.9)	0.07
Presence of asthma	75 (5)	15 (4)	0.48
Presence of migraine	23 (2)	9 (2)	0.22
Presence of (pre-)eclampsia	0	0	–
High BMI ^a	122 (11)	43 (15)	0.03
Current smoker ^b	376 (29)	83 (26)	0.36
Mean number of GP visits	11.5 (8)	13.5 (7)	0.85
Use of paracetamol	194 (13)	65 (18)	0.02
Use of NSAIDs	38 (3)	12 (3)	0.43

BMI body mass index, GP general practitioner, NSAIDs non-steroidal anti-inflammatory drugs, SD standard deviation

^a Data on BMI were missing for 877 patients

^b Data on smoking were missing for 528 patients

Table 3 Unadjusted and adjusted conditional odds ratios for the development of childhood asthma after exposure to acid-suppressive drug during pregnancy

	Cases ($N = 1,874$) N (%)	Controls ($N = 1,874$) N (%)	Unadjusted conditional OR (95 % CI)	Adjusted conditional OR (95 % CI) ^a
Exposure to any acid-suppressive drug	405 (22)	367 (20)	1.20 (1.00–1.45)	1.23 (1.01–1.51)
Subgroup of acid-suppressive drugs ^b				
PPIs or H2ra	42 (2.2)	33 (1.8)	1.36 (0.81–2.28)	1.72 (1.00–2.07)
PPI	13 (0.7)	7 (0.4)	2.20 (0.76–6.33)	2.76 (0.93–8.17)
H2ra	33 (1.8)	28 (1.5)	1.24 (0.70–2.2)	1.56 (0.85–2.90)
Other	378 (20.1)	347 (18.5)	1.17 (0.96–1.42)	1.16 (0.95–1.42)
Trimester ^c				
First/second	213 (11)	213 (11)	1.0 (0.77–1.21)	1.01 (0.79–2.08)
Third	304 (16)	267 (14)	1.25 (1.01–1.56)	1.29 (1.03–1.62)

CI confidence interval, OR odds ratio, PPI proton pump inhibitor, H2ra receptor antagonists

^a Adjusted for gender, birth order, age of the mother at birth and number of GP visits during pregnancy

^b In few pregnancies, more than one subgroup of drugs were prescribed

^c Women could take more than one prescription per trimester

therapy may have differential risks than non-exposed mothers such as genetic predisposition, smoking or other risk behaviours and co-morbidities that could be associated with asthma, and which may have led to confounding bias in previous studies [9–11], these factors were controlled in the study design. Importantly, treatment of gastroesophageal reflux disease (GERD) symptoms has been associated with improvement in asthma. Thus, prescriptions for acid-suppressing medication could be a proxy for presence of asthma in the mother, which itself is a risk factor for asthma development in the child. The current study design controls for this potential bias by having the same mother

for both siblings in each case–control pair. We examined samples of medical records of the mothers for information on additional potential confounding factors and took these into account by either matching or multivariate adjustments. By design, we showed that these measured risk factors were similarly distributed among exposed and unexposed and had only a small influence on the estimated associations. It is therefore highly unlikely that residual confounding by unmeasured factors could explain our findings.

There are also limitations to our study. Though odds ratios were materially elevated for PPIs and H2ra, the OR

was smaller overall, which suggests a class effect, but we had inadequate statistical power to formally test this. It is possible that we missed some exposures, because of over-the-counter use without prescription, though in the UK during pregnancy such exposures should be only a small proportion of all acid-suppressive drug use. In The Netherlands, for example, which has a similar healthcare system as the UK, use of over-the-counter drugs is low among pregnant women and we believe that this has had no major influence on our findings [24]. Also, we assumed that all prescribed medications were actually taken. Since exposure misclassification is likely random, this should not have materially affected our findings. Second, it is possible that we missed some children who had undiagnosed asthma because they did not seek medical attention, or mild asthma not treated chronically as was required by our definition including drug treatment. Overall, while such errors in identifying cases may lead to bias in estimating incidence rates, they will usually have little impact on ORs estimated from case-control studies. Further, some asthma cases might not have an allergic component. However, it is well known that this is a minority and more than 80 % of asthma is allergic. Importantly, potential selection bias was also minimized because children were followed for at least 3 years and both cases and controls were required to have the same length of follow-up. Since information on the conception date was unavailable to the researchers, in accordance with other pregnancy studies, we applied a standardized period of 335 days to define the pregnancy duration [18]. Such standardization may also have led to some small amount of exposure misclassification, which could have resulted in a minimal overestimation of actual use. By design, we could only examine families with two or more children and those without teratogen use. Our findings do not necessarily apply to smaller families or pregnant women who use teratogens. Of note, it is not known how the ORs from a crossover design would correspond to the actual risk in the general population of acid-suppressant users as measured, for example, using a cohort or conventional case-control design. By definition, in the crossover design, each case and matched control had the same mother and thus differences in mothers' susceptibility were controlled. Hence, the study population may have been a subsample of the population where the effect of acid-suppressive drugs may be stronger than in the general pregnant population. Though by design the potential confounding effect of asthma in the mother is largely controlled for, it is possible for a woman to have a period of particularly poor asthma control during one of the two pregnancies, leading to an increased risk of childhood asthma and acid-suppressive drug use in only one of the two offspring. Data to control for asthma severity are not routinely available, and future studies should examine the

potential impact of disease status and also look at the exposure pre-pregnancy-outcome association as a negative control. Indeed, in our prescription database study, a pre-pregnancy exposure-outcome association was absent [12].

4.3 Comparison with Other Studies and Hypotheses

The observed association between prenatal exposure to acid-suppressive drug and asthma in our study is consistent with the findings of Dehlink et al. [9], Andersen et al. [10] and Källén et al. [11] and also with findings from an unpublished study using a case-crossover design in the University Groningen pregnancy database in which we defined cases as toddlers who were prescribed asthma medications at least two times before the age of 5 years [12]. Since we showed the minimal influence of confounding in the associations, the validity of earlier reports is supported by our findings. The precise mechanisms by which acid-suppressive drugs may cause asthma are hypothetical. It has been proposed that neutralized gastric acid levels prevent adequate digestion of antigens in the adult stomach. While antigens normally degrade into oligopeptides to enter the gastrointestinal tract, these can now induce a T-helper (Th)-2 response and immunoglobulin (Ig)-E sensitization of the immune system [25–27]. If crossing the placenta, these antigens could induce allergic sensitization of the foetus [28]. This hypothesis is supported by a study in pregnant mice showing a Th2-dominant immune response in the offspring caused by gastric acid suppression [29]. The development of the foetal immune system is also influenced by the allergic state of the mother. The dominant Th2 cytokine phenotype in allergic mothers was present in the cord blood, which could promote an allergy-prone phenotype in the foetus [30]. Also, maternal IgE can cross foetal membranes and sensitize immune cells of the foetus to allergens [31]. Alternatively, it may be hypothesized that the development of lung tissue may directly be damaged by these drugs by another unknown mechanism. However, the first hypothesis seems more likely given that the associations in our study were significant, especially during the later trimester, in which the immune system in particular develops, but more study, for example, of the mechanism or development of other atopic conditions in relation to acid-suppressive drug use, is now warranted.

5 Conclusion

These findings lend support to the emerging evidence that exposure to acid-suppressive drugs during pregnancy is associated with childhood asthma. More basic research is now warranted to investigate the mechanisms.

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Authors' contributions EH initiated and designed the study, performed the study, analysed and interpreted the data and drafted the manuscript; BM participated in the design as a pharmaceutical expert and reviewed the manuscript; CCMSV participated in the design of the study as an expert in pharmaceutical research and reviewed the analyses and manuscript; SSJ participated in the design of the study, and supervised the data collection, analysis and report. All authors commented on the manuscript and approved the final manuscript. The corresponding author had full access to all data and the final responsibility for the decision to submit for publication.

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Conflict of interest All authors (Eelko Hak, Bianca Mulder, Nynke CM Schuiling-Veninga, Tjalling W. de Vries, Susan S Jick) have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare the following: they had support from the department of Pharmacy, University Groningen, for the submitted work; no financial relationships with any organisation that might have an interest in the submitted work in the previous 3 years; and no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval The study was approved by the Independent Scientific Advisory Committee (ISAC) within the UK Medicines and Healthcare Products Regulatory Agency.

Data sharing Not applicable.

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